

## TENT COOPERATION TRE, Y 111394

From the INTERNATIONAL BUREAU

**PCT****NOTIFICATION OF ELECTION**

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents  
 United States Patent and Trademark  
 Office  
 Box PCT  
 Washington, D.C.20231  
 ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

<b>Date of mailing</b> (day/month/year) 17 February 2000 (17.02.00)	<b>Applicant's or agent's file reference</b> 079498/0120
<b>International application No.</b> PCT/US99/12799	<b>Priority date</b> (day/month/year) 12 June 1998 (12.06.98)
<b>International filing date</b> (day/month/year) 11 June 1999 (11.06.99)	
<b>Applicant</b> NARDONE, Glenn	

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

12 January 2000 (12.01.00)

in a notice effecting later election filed with the International Bureau on:

\_\_\_\_\_

2. The election  was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer  Diana Nissen
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>079498/0120</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/US 99/12799</b>	International filing date (day/month/year) <b>11/06/1999</b>	(Earliest) Priority Date (day/month/year) <b>12/06/1998</b>
Applicant <b>INTERGEN COMPANY et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of **2** sheets.

It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
  - the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :
  - contained in the international application in written form.
  - filed together with the international application in computer readable form.
  - furnished subsequently to this Authority in written form.
  - furnished subsequently to this Authority in computer readable form.
  - the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
  - the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2.  **Certain claims were found unsearchable** (See Box I).

3.  **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

- the text is approved as submitted by the applicant.
- the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- the text is approved as submitted by the applicant.
- the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

- as suggested by the applicant.
- because the applicant failed to suggest a figure.
- because this figure better characterizes the invention.

None of the figures.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/12799

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 02449 A (ONCOR INC) 22 January 1998 (1998-01-22) ----	
A	EP 0 601 889 A (MAINE MEDICAL CENTER RES) 15 June 1994 (1994-06-15) ----	
A	EP 0 566 751 A (HOFFMANN LA ROCHE) 27 October 1993 (1993-10-27) -----	

Further documents are listed in the continuation of box C

Patent family members are listed in annex

### "Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

21 December 1999

13/01/2000

Name and mailing address of the ISA

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Fax: (+31-70) 340-3016

Authorized officer

Bardilli, W

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/12799

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9802449	A	22-01-1998	US	5866336 A	02-02-1999
			AU	3728597 A	09-02-1998
			CA	2260973 A	22-01-1998
			EP	0912597 A	06-05-1999
EP 0601889	A	15-06-1994	US	5607834 A	04-03-1997
EP 0566751	A	27-10-1993	CA	2090904 A	24-09-1993
			DE	69207580 D	22-02-1996
			DE	69207580 T	08-08-1996
			DK	566751 T	04-03-1996
			ES	2082256 T	16-03-1996
			GR	3019617 T	31-07-1996
			IE	72498 B	23-04-1997
			JP	6007199 A	18-01-1994
			US	5573906 A	12-11-1996

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>C12Q 1/68</b>		A3	(11) International Publication Number: <b>WO 99/64432</b>
			(43) International Publication Date: 16 December 1999 (16.12.99)
(21) International Application Number: PCT/US99/12799		(81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).	
(22) International Filing Date: 11 June 1999 (11.06.99)			
(30) Priority Data: 60/089,119 12 June 1998 (12.06.98) US		Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 60/089,119 (CIP) Filed on 12 June 1998 (12.06.98)		(88) Date of publication of the international search report: 24 February 2000 (24.02.00)	
(71) Applicant (for all designated States except US): INTERGEN COMPANY [US/US]; Two Manhattanville Road, Purchase, NY 10577 (US).			
(72) Inventor; and			
(75) Inventor/Applicant (for US only): NARDONE, Glenn [US/US]; 11735 Stuart Mill Road, Oakton, VA 22124 (US).			
(74) Agents: BENT, Stephen, A. et al.; Foley & Lardner, Suite 500, 3000 K Street N.W., Washington, DC 20007-5109 (US).			

(54) Title: MULTI-FLUORESCENT HAIRPIN ENERGY TRANSFER OLIGONUCLEOTIDES

(57) Abstract

An oligonucleotide, labeled with a molecular energy transfer trio and containing two sequences capable of hairpin formation, is used in the detection of two targets by irradiation with a single wavelength of light. One of the two sequences contains an energy donor and a first energy acceptor, and the other sequence contains a second energy acceptor. The donor is in close proximity to the second acceptor only if the hairpin is formed, while the donor is always in close proximity to first acceptor. A sample is assayed, using this oligonucleotide in conjunction with another oligonucleotide which contains the donor fluorophore and the quencher, arranged as described above, but which lacks the acceptor fluorophore. The present oligonucleotide and the other oligonucleotide are specific to first and second targets, respectively. If a sample contains the first and second targets, then hairpin formation is prevented after each oligonucleotide is incorporated into a target amplification product or hybridized to a target. Subsequent irradiation of the sample with the single wavelength of light which excites the donor fluorophore, but not the acceptor fluorophore, causes two distinctive signals to be generated. The first signal is emitted by the second fluorophore of the present oligonucleotide, while the second signal is emitted by the first fluorophore of the other oligonucleotide. Thus, the first and second targets are detected when one observes the first and second signals, respectively.

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/12799

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 6 C12Q/68

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 02449 A (ONCOR INC) 22 January 1998 (1998-01-22) ---	
A	EP 0 601 889 A (MAINE MEDICAL CENTER RES) 15 June 1994 (1994-06-15) ---	
A	EP 0 566 751 A (HOFFMANN LA ROCHE) 27 October 1993 (1993-10-27) -----	

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

**Special categories of cited documents:**

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

21 December 1999

13/01/2000

Name and mailing address of the ISA

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Authorized officer

Bardilli, W

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat'l Application No

PCT/US 99/12799

Patent document cited in search report	Publication date	Patent family member(s)			Publication date
WO 9802449	A 22-01-1998	US AU CA EP	5866336 A 3728597 A 2260973 A 0912597 A		02-02-1999 09-02-1998 22-01-1998 06-05-1999
EP 0601889	A 15-06-1994	US	5607834 A		04-03-1997
EP 0566751	A 27-10-1993	CA DE DE DK ES GR IE JP US	2090904 A 69207580 D 69207580 T 566751 T 2082256 T 3019617 T 72498 B 6007199 A 5573906 A		24-09-1993 22-02-1996 08-08-1996 04-03-1996 16-03-1996 31-07-1996 23-04-1997 18-01-1994 12-11-1996

## PATENT COOPERATION TREATY

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 079498/0120	<b>FOR FURTHER ACTION</b>	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US99/12799	International filing date (day/month/year) 11/06/1999	Priority date (day/month/year) 12/06/1998
International Patent Classification (IPC) or national classification and IPC C12Q1/68		
Applicant INTERGEN COMPANY et al.		
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>		
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> <li>I <input checked="" type="checkbox"/> Basis of the report</li> <li>II <input type="checkbox"/> Priority</li> <li>III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</li> <li>IV <input type="checkbox"/> Lack of unity of invention</li> <li>V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</li> <li>VI <input type="checkbox"/> Certain documents cited</li> <li>VII <input checked="" type="checkbox"/> Certain defects in the international application</li> <li>VIII <input checked="" type="checkbox"/> Certain observations on the international application</li> </ul>		

Date of submission of the demand 12/01/2000	Date of completion of this report 29.06.2000
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Bardili, W Telephone No. +49 89 2399 2132



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US99/12799

**I. Basis of the report**

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

**Description, pages:**

1-17                   as originally filed

**Claims, No.:**

1-74                   as originally filed

2. The amendments have resulted in the cancellation of:

the description,       pages:  
 the claims,           Nos.:  
 the drawings,         sheets:

3.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Yes:      Claims 1-74
	No:      Claims
Inventive step (IS)	Yes:      Claims 1-74
	No:      Claims
Industrial applicability (IA)	Yes:      Claims 1-74
	No:      Claims

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US99/12799

2. Citations and explanations

**see separate sheet**

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:

**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/12799

**Re Item V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

The citations are:

D1: WO-A-98 02 449 A1

D2: EP 601 889 A2

D3: EP 566 751 A1.

D1 details hairpin oligonucleotides useful as primers in nucleic acid amplification comprising an energy donor and an energy acceptor. The acceptor is a quencher which is located in close proximity to the donor only when the hairpin structure is intact (cf. page 11 of the citation). When the primer is incorporated into the amplification product its configuration changes, quenching is eliminated, and the fluorescence of the donor moiety may be detected. D2 and D3 disclose similar subject-matter.

The claimed oligos are novel owing to the fact that one donor moiety and two acceptor moieties are linked to the oligo in a certain arrangement as indicated in claim 1.

The technical problem to be solved by the present invention can be seen in a process to detect two target oligonucleotides in one sample using a fluorometric assay wherein only one wavelength of light is required to detect each of the targets independently from each other. The available prior art neither addresses that problem nor makes suggestions how it could be solved. Inventive step is therefore acknowledged.

**Re Item VII**

**Certain defects in the international application**

The documents D1, D2 and D3 should be mentioned in the description of the application as prior art pursuant to Rule 5.1 ii) PCT.

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/12799

**Re Item VIII**

**Certain observations on the international application**

The expression *first acceptor* and *second acceptor* in the claims is not deemed appropriate to fully describe the claimed subject-matter. The first acceptor apparently is a moiety capable of absorbing energy and producing a detectable signal by emitting light whereas the second acceptor appears to be a quencher incapable of producing a detectable signal by emission of light. The claim language, however, is entirely silent on that matter. The application therefore does not satisfy the requirements of Article 6 PCT.